Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Fedratinib (reassessment after the deadline: myelofibrosis)

of 21 August 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must

be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient fedratinib (Inrebic) on 12 March 2021. The resolution of 2 September 2021 adopted by the G-BA in this procedure was set a deadline until 1 March 2025 for patient population b) (adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who have been treated with ruxolitinib, for the treatment of disease-related splenomegaly or symptoms).

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Inrebic recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 24 February 2025.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 02 June 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA have adopted their resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G25-11) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA have evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of fedratinib.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Fedratinib (Inrebic) in accordance with the product information

Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

Therapeutic indication of the resolution (resolution of 21 August 2025):

Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who have been treated with ruxolitinib.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of fedratinib is assessed as follows:

b) adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with Ruxolitinib, treatment of disease-related splenomegaly or symptoms

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company submitted the data from the FREEDOM2 study for the new benefit assessment after expiry of the deadline. The FREEDOM2 study is a multicentre, randomised, open-label phase III study. The study was divided into a comparative treatment phase of at least 24 weeks (6 cycles), in which fedratinib was compared with the best available therapy (BAT), followed by a follow-up phase and a survival follow-up. Ruxolitinib (77.6%), transfusions with red blood cells (28.4%) and hydroxyurea (17.9%) were predominantly used as BAT. After the end of the 6th cycle of the treatment phase, a treatment switch from BAT to fedratinib was possible for subjects in the control arm and was carried out by the majority of patients. The study was conducted at 78 study sites in Europe, Asia and Australia. The start of the study was on 9 September 2019.

Adults with intermediate-risk-2 or high-risk primary myelofibrosis (MF), post polycythaemia vera MF or post essential thrombocythaemia MF with splenomegaly and symptoms who had previously been treated with ruxolitinib were enrolled in the study. A total of 201 subjects were enrolled and randomised in a 2:1 ratio, stratified by spleen size on palpation (< 15 cm versus ≥ 15 cm under the left costal arch), platelet count (≥ 50 to < 100 x 10^9/l versus ≥ 100 x 10^9/l) and previous ruxolitinib treatment (refractory/ relapsed versus intolerance).

The pre-specified data cut-off from 27 December 2022 was available for the benefit assessment. This data cut-off took place after the last randomised subject had completed cycle 6. The data from the 24-week treatment phase were used for the benefit assessment. The primary endpoint of the study was the reduction in spleen volume by ≥ 35%.

On the implementation of the time limit requirements

The initial assessment was based on the results for the patient population b) of the single-arm JAKARTA-2 study. According to the justification for the resolution of 2 September 2021, the reason for the time limit was the lack of significant data on patient-relevant endpoints for patients pretreated with ruxolitinib for the benefit assessment. Furthermore, the JAKARTA-2 study was discontinued prematurely due to the occurrence of Wernicke's encephalopathy, which led to a short observation period.

In view of the fact that data - possibly relevant for the assessment of the additional benefit - from the ongoing FREEDOM2 clinical study comparing fedratinib with BAT were expected at the time of the resolution, the results on all patient-relevant endpoints of the FREEDOM2 study should be presented for the new benefit assessment.

The time limit requirements are considered to have been implemented.

On the study results:

Mortality

The endpoint of overall survival is operationalised as the time from randomisation to death, regardless of the cause of death. There was no statistically significant difference between the treatment arms.

Morbidity

Spleen response using MRI/CT

In the FREEDOM2 study, spleen response was the primary endpoint. The spleen response rate was defined as the percentage of subjects with a spleen volume reduction by ≥ 35% measured by magnetic resonance imaging (MRI) or computed tomography (CT) at week 24 compared to baseline. There was a significant advantage for the fedratinib arm.

Symptomatology response using MFSAF

Symptomatology was assessed in the FREEDOM2 study using the MFSAF v. 4.0 (Myelofibrosis Symptom Assessment Form). The MFSAF v. 4.0 comprises seven items on the disease-specific symptoms of fatigue (exhaustion, tiredness), night sweats or feeling hot, itching, abdominal conditions (feeling of pressure in the upper abdomen), pain below the left costal arch, fullness shortly after starting to eat and bone pain (not joint or arthritis pain).

The endpoint was operationalised as a reduction by ≥ 50% of the total symptom score (TSS) compared to the baseline value.

According to the IQWiG methods paper, a response threshold of 15% or more of the scale range can be assumed to indicate a change that can be perceived with sufficient certainty (scale range of the MFSAF-TSS = 70 points, 15% corresponds to 10.5 points). According to this response threshold, a reduction of the MFSAF-TSS by ≥ 50% would represent an improvement that can be perceived with sufficient certainty if the baseline value of the MFSAF-TSS of the patients is at least 21 points.

In contrast, the baseline distribution data in the MFSAF-TSS show that 25% of the patient population in both the control and intervention arms have a baseline value of 16 or less. In order to reach the response threshold of 10.5 in this quarter of the patient population as well, responders would have to improve by at least 66%, for which the pharmaceutical company did not provide any evidence in the dossier. It can therefore be assumed that with a 50% reduction in MFSAF-TSS, a relevant percentage (> 20%) of patients do not reach the response

threshold of an improvement by 10.5 points. Therefore, this evaluation of the MFSAF-TSS cannot be used for the benefit assessment.

Despite this criticism of the evaluations in the pharmaceutical company's dossier presented in the benefit assessment, no analyses corresponding to the response threshold of 15% (10.5 points) were submitted by the pharmaceutical company as part of the statements on the benefit assessment.

This means that only the continuous evaluations for the MFSAF-TSS can be used for the assessment. These showed a statistically significant difference in favour of fedratinib. A p value and a Hedges' g were not presented by the pharmaceutical company.

In order to assess the clinical relevance of the significant advantage of the MFSAF-TSS, the standardised mean difference (Hedges' g) was calculated by the medical consultation. However, the 95% confidence interval of the standardised mean difference (Hedges' g) is within the irrelevance threshold (-0.2 to 0.2), so that it cannot be concluded with sufficient certainty that the observed effect is clinically relevant.

The risk of bias is estimated as high due to the open-label study design and the high percentage of missing values.

Conclusion on spleen response and symptomatology response using MFSAF

A long-lasting reduction in the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms for the patients is considered to be patient-relevant. In the present case, the spleen response was collected by means of imaging procedures. Although the continuous evaluations for the MFSAF-TSS show a statistically significant difference in favour of fedratinib, no clinical relevance can be derived from this.

As a result, no relevant difference for the benefit assessment can be derived for the symptomatology, which is why the spleen response as the primary endpoint of the FREEDOM2 study is only presented additionally.

Symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS)

In the study, further data on symptomatology were collected using the symptom scales of the EORTC QLQ-C30 questionnaire and on health status using the EQ-5D VAS. The data at the end of cycle 6, in which the required return rate was not achieved, are available for the benefit assessment.

The required return rates of more than 70% was only achieved up to cycle 4. The data required for the evaluation was not submitted subsequently.

The available data from the EQ-5D VAS and the EORTC QLQ-C30 can therefore not be evaluated.

Quality of life

Patients' quality of life was assessed in the FREEDOM2 study using the EORTC QLQ-C30. Reference is made to the above statements on the endpoint of symptomatology.

The available data from the EORTC QLQ-C30 cannot be evaluated.

Side effects

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs)

In terms of occurrence of serious AEs, there was no statistically significant difference between the two treatment arms.

Severe AEs (CTCAE grade ≥ 3)

For severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference to the disadvantage of fedratinib.

Therapy discontinuation due to AEs

For the endpoint of therapy discontinuation due to AEs, there were no statistically significant differences between the treatment arms.

Specific AE

In detail, the AEs of special interest showed a statistically significant disadvantage to the disadvantage of fedratinib in the endpoints "Thrombocytopenia with CTCAE grade 3 or 4", "Thiamine levels below the normal range with or without signs or symptoms of Wernicke's encephalopathy" and "Encephalopathy, including Wernicke's encephalopathy or suspected cases of Wernicke's encephalopathy, associated with thiamine levels below the normal range". Due to the lack of effect estimators for the severe AEs and SAEs according to MedDRA, further specific AEs cannot be assessed with regard to the individual events.

Overall assessment

Data from the FREEDOM2 study, which compared fedratinib with Best Available Therapy (BAT), are available for the benefit reassessment of fedratinib after expiry of the deadline for adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis treated with ruxolitinib. Results from this study are available on mortality, morbidity, quality of life and adverse events.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

In the morbidity endpoint category, results are available on spleen response, symptom response, assessed using MFSAF, as well as symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS).

For the spleen response, assessed using imaging procedures (MRI/CT), there was a statistically significant difference in favour of fedratinib. With regard to the symptom response using MFSAF, the available continuous evaluations show a statistically significant difference in favour of fedratinib. A long-lasting reduction in the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms for the patients is considered to be patient-relevant. The 95% confidence interval of the standardised mean difference (Hedges' g) of the MFSAF-TSS is within the irrelevance threshold (-0.2 to 0.2), so that it cannot be concluded that the observed effect in the symptom response using MFSAF is clinically relevant. As a result, no relevant difference can be determined for the symptomatology.

No suitable data are available on symptomatology (assessed using EORTC-QLQ-C30) and health status (assessed using EQ-5D-VAS) due to a high percentage of missing values. This also applies to the data on health-related quality of life (collected using EORTC QLQ-C30).

In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity.

In terms of side effects, there was a statistically significant disadvantage of fedratinib for severe AEs (CTCAE grade ≥ 3). For serious AEs and discontinuations due to AEs, there were no statistically significant differences. In detail, there were also disadvantages for individual adverse events of special interest.

For the endpoint category side effects, an overall disadvantage of fedratinib can be observed.

In the overall assessment, a non-quantifiable additional benefit of fedratinib is identified for the treatment of disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, since the scientific data does not allow quantification.

Significance of the evidence

The data from the 24-week treatment phase of the open-label, randomised phase III FREEDOM2 study were used for the present benefit assessment.

The risk of bias of the FREEDOM2 study is essentially assessed as high due to the open-label study design.

For the endpoint "Symptom response using MFSAF", the high percentage of missing values (fedratinib arm: 33.1%; BAT arm: 31.2%) led to an additional risk of bias. Due to the similar distribution of missing values in both arms, the endpoint was nevertheless used for the benefit assessment, taking the limitation into account.

In the overall assessment, the result is a hint for the identified additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient fedratinib after expiry of the time limit of the resolution of 2 September 2021. The time limit related exclusively to the patient group "adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, for the treatment of disease-related splenomegaly or symptoms".

The therapeutic indication assessed here is as follows:

"Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who have been treated with ruxolitinib."

Data from the multicentre, randomised, open-label, phase III FREEDOM2 study, in which fedratinib was compared with Best Available Therapy (BAT), were available for the benefit assessment .

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity.

Based on the results on side effects, there was a disadvantage of fedratinib in the endpoint of severe AEs (CTCAE grade ≥ 3). In detail, there were also disadvantages for individual adverse events of special interest.

In the overall assessment, a non-quantifiable additional benefit of fedratinib is identified, since the scientific data does not allow quantification.

Relevant uncertainties result mainly due to the open-label study design and the high percentage of missing values in the endpoint "Symptom response using MFSAF".

The reliability of data of the additional benefit identified is classified as a "hint".

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA base their resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The patient numbers are subject to uncertainties.

To determine the number of patients with myelofibrosis who have been pretreated with ruxolitinib, the pharmaceutical company proceeded analogously to the previous resolution on fedratinib (resolution of 2 September 2021). The pharmaceutical company derived the percentage of the total population from the prescription data for ruxolitinib from 2013. At that time, ruxolitinib was only approved for the treatment of patients with myelofibrosis. For the present resolution, the pharmaceutical company updated the information on the total population and the SHI percentage.

The data were subject to limitations due to the lack of up-to-date prescription data for ruxolitinib and the potentially altered market penetration of ruxolitinib.

2.3 Requirements for a quality-assured application

As a result of the present benefit assessment procedure, the requirements for a quality-assured application already established by resolution of 2 September 2021 remain in place.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2025).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fedratinib	Continuously, 1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Fedratinib	400 mg	400 mg	4 x 100 mg	365	1460 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Fedratinib 100 mg	120 HC	€ 3,810.55	€ 1.77	€ 214.33	€ 3,594.45
Abbreviations: HC = hard capsules					

LAUER-TAXE® last revised: 1 August 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Additionally required SHI services for the application of the medicinal product to be evaluated according to the product information and patient information leaflet are given by the necessity of determining the thiamine level prior to therapy initiation. According to the product information, thiamine levels should be assessed at baseline and at regular intervals

thereafter, e.g. monthly for the first 3 months and every 3 months thereafter (and as clinically indicated). Accordingly, 7 determinations per year are assumed.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed:							
Fedratinib							
Determination of the thiamine level							
Quantitative chromatographic determination(s) of one or more substance(s) - Vitamins GOP 32306	-	-	-	-	€ 20.52	7	€ 143.64

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the

pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as

part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of

medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

b) adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, for the treatment of disease-related splenomegaly or symptoms

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for fedratinib (Inberic); Inrebic® 100 mg hard capsules; last revised: February 2025

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 24 February 2025, the pharmaceutical company submitted a dossier for the benefit assessment of fedratinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 2 June 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 June 2025.

The oral hearing was held on 7 July 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 August 2025, and the draft resolution was approved.

At their session on 21 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	2 July 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 July 2025	Conduct of the oral hearing
Working group Section 35a	16 July 2025 6 August 2025	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 August 2025	Concluding discussion of the draft resolution
Plenum	21 August 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 August 2025

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken